

ARGUMENTS/REMARKS

The application has been amended. Claims 1-17 are pending in the application. Claims 4-17 have been withdrawn from consideration. Claim 1 has been amended to better clarify the invention. Also, new claim 19 has been added. Support for the amendments can be found, for example, on page 2, lines 19-22; on page 5, lines 9-17; in Example 1, in Table 6 on page 19 and in Table 7 on page 22. Accordingly, claims 1-3 are currently under examination. No new matter has been added by way of the amendments.

Claim Rejection under 35 U.S.C. §103

Claims 1-3 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Johnson *et al.* (Journal of Virology, Apr. 1998, Vol. 72, No. 4, pages 2871-2880) in view of Firestone *et al.* (Virology, 1996. Vol. 225, pages 419-422. Article No. 0618, Short Communication).

The Office Action alleged that it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to identify a high glycoprotein producing RSV. The Office Action further alleged that a person of ordinary skill in the art would have been motivated because Johnson teaches the importance of the glycoprotein F and how to measure the glycoprotein, and Firestone teaches a comparison of attenuated RSVs to the wild-type RSV, and as such, one reasonably would have expected success because of the teachings of Johnson and Firestone.

The invention, as currently claimed, is directed to a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F when compared to parent strain A2. The method includes: providing a eukaryotic cell culture, infecting the cell culture with a live, attenuated RSV strain at 30°C; harvesting the infected cell culture; solubilizing the F protein in the harvested culture; and subsequently determining the glycoprotein F concentration in the harvested culture, wherein at least a five-fold increase in glycoprotein F concentration produced when the attenuated RSV strain is grown in the cell culture at 30° C is an indication that the attenuated strain produces high yields of RSV F glycoprotein when

compared with the parent A2 strain grown at 37°C. The RSV mutant strain is cpts-248/404. The eukaryotic cell cultures are VERO, MRC-5, FRhL, CEF or PER.C6 cell cultures.

Applicants submit that the combination of Johnson and Firestone fails to disclose or suggest the subject matter of the amended claims.

Johnson does not disclose a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV glycoprotein F, as claimed. Rather, Johnson, as a whole, is primarily concerned with the effects of RSV G priming on immune responses (Abstract). The products used for Johnson's priming immunization study included vaccinia virus constructs expressing RSV F (vac F), wild-type RSV G (vvWTG), membrane-anchored RSV G (vvM481) and secreted RSV G (vvM48) (Table 1 and 1st paragraph of Results). These constructs are different from the claimed invention, which employs a live attenuated RSV.

Moreover, Johnson only discloses a method of purifying secreted RSV G and measuring the RSV G protein in the chromatographic fractions (2nd paragraph of material and methods). Johnson's secreted G protein is obtained from the culture supernatant of cells infected with a vaccinia virus construct (vvM48). Johnson's glycoprotein is not obtained by infecting a cell culture with a live attenuated RSV strain nor is Johnson's glycoprotein solubilized, as claimed.

In fact, the Examiner has acknowledged that Johnson does not teach an attenuated RSV. Johnson also does not teach or suggest an attenuated respiratory syncytial virus (RSV) strain that produces a five fold increase in the amount of glycoprotein F, as claimed. Nor does Johnson teach or suggest any methods comprising growing a strain of RSV at 30°C, as claimed.

The Firestone reference fails to make up for the deficiencies of Johnson.

Firestone teaches the nucleic acid sequence of the RSV mutant strain cpts-248/404. The sequence analysis conducted by Firestone was done in an attempt to

determine which nucleotides played a role in temperature sensitivity and/or attenuation of the virus. In contrast to the claimed invention, Firestone does not teach or suggest measuring the levels of the F glycoprotein produced by the mutant *cpts-248/404* strain at 30°C during the course of their work, nor any difference in the levels of the F glycoprotein produced with the parent A2 strain. The Firestone reference merely teaches the sequence differences between the various proteins of the parent A2 strain and the mutant strains of the virus to determine whether any of the differences observed could be related to, or associated with, temperature sensitivity or to the attenuation of the virus.

The Office Action alleged that Firestone teaches a *cpts-248/404* mutant, which differs from its wild-type RSV strain A2 by increased G when passaged in VERO cell culture. The Office Action further alleged that Firestone compares F content in the live attenuated RSV strain to the parent A2 strain, and that Firestone teaches a *cpts-248/404* mutant which differs from its wild type RSV strain by increased G and F gene content.

Applicants respectfully disagree with the Office Action's interpretations of Firestone. Firestone only discloses the development of a G nucleotide to C nucleotide change at nucleotide 4 of the 3' end leader sequence during passage of the *cpts-248/404* virus (page 422). Firestone does not disclose or suggest an increase in G when passaged, as alleged. Specifically, Firestone discloses neither an increase in G nucleotide, nor an increase in G glycoprotein during passage of the mutant virus. Moreover, the 3' end leader sequence containing the G or C nucleotide at position 4 is not even a G gene sequence. Rather, it is a non-coding sequence. Firestone further discloses that the *cpts-248/404* viruses that differed at nucleotide 4 (G or C) had the same level of temperature sensitivity of replication and the same level of replication in the upper and lower respiratory tract of mice, and suggests that heterogeneity at this nucleotide is not even clinically relevant (Table 2, page 421-422 joining paragraph and Abstract).

Also, Applicants could not find any teaching in the Firestone reference regarding an increase in "F gene content" by this mutant strain as compared to the parent A2 strain, as alleged on page 4 of the Office Action. Firestone merely discloses changes in

the F gene (at nucleotide positions 6313 and 7228) between the parent A2 strain and the cpts-248/404 mutant strain resulting in amino acid substitutions (at positions 218 and 523) in the F protein on page 421, Table 1. There is no data provided by Firestone that teaches or suggests the enhanced production of the F glycoprotein by the mutant strain when grown at 30°C, as compared to the parent A2 strain grown at 37°C, as currently claimed.

To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art references, when combined, must teach or suggest all the claim limitations. Second, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the teachings within the references. Third, there must be a reasonable expectation of success in achieving the claimed invention. See MPEP § 2143.

The arguments advanced in the Office Action fail to meet all of these criteria for the current invention, as presently claimed. More particularly, any rejection based on Johnson and Firestone, in combination, fails for at least the following reasons.

There is no disclosure or suggestion in the references that when combined teach a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F when grown at 30°C as compared to the amount of glycoprotein F produced by the parent A2 strain grown at 37°C.

There is no motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings found in the cited references to achieve Applicants' claimed invention. Assuming *arguendo* that Johnson generally discloses the importance of the F glycoprotein and how to measure the G glycoprotein in chromatographic fractions, there is still nothing in the cited references which discloses or suggests that changes in the F gene or F protein have any effect on temperature sensitivity or replication, nor that the mutant RSV strain has enhanced production of the F glycoprotein at 30°C.

Furthermore, the outcome observed through use of the methods of the invention were not known, and could not be predicted based on the cited references, since it was only at the time of the present invention that a mutant strain *cpts-248/404*, when grown at 30°C showed an unexpected five fold increase in production of the F glycoprotein as compared to the amount of glycoprotein F produced by the parent A2 strain grown at 37°C.

The references cited by the Examiner when combined do not teach or suggest the subject matter defined in amended claim 1. In particular, they do not teach any increase in the F glycoprotein by the RSV strains tested, and more particularly, they do not teach a five fold increase in the F glycoprotein by strain *cpts-248/404* at 30° C in any of the cell cultures as currently claimed. Furthermore, neither of the references cited by the Examiner, or the knowledge generally available to one of ordinary skill in the art, would have provided any motivation to combine the teachings of Johnson in view of Firestone in order to achieve the presently claimed invention. More specifically, the references cited by the Examiner would not have suggested to one of skill in the art that a *cpts-248/404* mutant that replicates poorly in cells at 37°C, could produce a five fold increase in the F glycoprotein at 30°C, thus making it a highly desirable candidate for vaccine production. In fact, one might predict no difference in the production of F glycoprotein between the parent virus cultured at 37°C and the mutant virus at 30°C based on the teachings of Firestone. For instance, Table 2 of Firestone suggests that the two *cpts-248/404* mutant viruses exhibited about the same level of replication at 32°C as did the parent RSV A2 strain at 37°C. See, for example, the virus titers of 7.0 and 6.3, respectively, for 248/404-4G and 248/404-4C at 32°C, versus a virus titer of 6.0 for RSV A2 at 37°C.

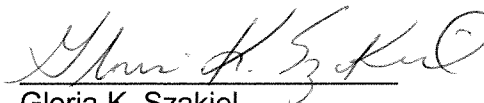
Therefore, Applicants submit that claim 1 is not rendered obvious by Johnson in view of Firestone. Each of claims 2-3 and new claim 19 depend from the subject matter of claim 1. Thus, the patentability of each of claims 2-3 and 19 under 35 U.S.C. § 103(a) necessarily follows from the non-obviousness of claim 1. Applicants respectfully request that the rejection of claims 1-3 be withdrawn.

Summary

Applicants have fully responded to the final Office Action. It is respectfully submitted that the application is in condition for allowance. Favorable action on the merits is requested. Should the Examiner have any questions or concerns regarding this amendment and response, the Examiner is respectfully invited to contact the undersigned at the telephone number set forth below. No additional fees are believed to be due in connection with this submission. However, if any fees are due, the Commissioner is hereby authorized to charge them to Deposit Account No. 01-1425.

Respectfully submitted,

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